Abortion Pill Investigated in Four California Deaths

The FDA warns patients as federal, state and L.A. County agencies try to trace deadly infections.

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Health officials are investigating whether there are any links in the cases of four California women — at least two in Los Angeles County — who have died since 2003 of massive infection after taking the so-called abortion pill, RU-486, and a follow-up drug.

The state and federal probe follows an announcement last month by the Food and Drug Administration, after the June death of a Sherman Oaks woman, warning doctors and patients of the potential for serious bacterial infection under certain circumstances.

At the heart of the inquiry in California are why and how the deadly infections developed and whether more women might have been harmed.

"That's something we don't have an explanation for right now," said Dr. L. Clifford McDonald, an epidemiologist with the Centers for Disease Control and Prevention, which is investigating the deaths along with the Food and Drug Administration, the California Department of Health Services and the Los Angeles County Department of Health Services.

The FDA is also working with the makers of the two drugs to see if they were contaminated with an unusual bacterium found in the bloodstream of two of the women who died. Complicating matters, neither woman showed all of the usual symptoms of an infection.

The medical mystery in California is fueling the already charged debate over the risks, rights and morality of abortion.

RU-486, prescribed under the brand name Mifeprex, was approved by the FDA in 2000 over the strong objections of many abortion opponents. In recent weeks, opponents of the RU-486 regimen have renewed their call for the passage of Holly's Law, which would take the drug off the market in the U.S., arguing that there is no way it can be administered without risk.

The proposed legislation was named after 18-year-old Holly Patterson of Livermore, Calif., the first U.S. woman to die of infection after a nonsurgical abortion in 2003. The procedure is often called a medical abortion.

"We should be just as concerned about women's safety as we are about their rights," said Wendy Wright, senior policy director for Concerned Women for America, which has been working to get the drug prohibited. "I've been stunned by the comments … that some women have to pay the price of death so that women can have abortions."

Vicki Saporta, president of the National Abortion Federation, said such concerns were vastly

overblown. "There has been no causal relationship established between the medical abortion and the subsequent infection," she said. "This is a very, very rare occurrence…. Childbirth is 10 to 13 times riskier than having an abortion, either medical or surgical."

Supporters also say the drug combination is the safest means of terminating an early pregnancy, pointing to the World Health Organization's recent listing of the drugs as essential to healthcare needs in developing countries.

Mifeprex, which is administered in a clinic or doctor's office, is taken orally up to 49 days after a woman becomes pregnant. Several days later, the drug misoprostol is given. The first drug blocks a hormone necessary for a pregnancy to continue; the second causes contractions of the uterus.

The drugs are different from emergency contraception, which is also controversial. The "morning after pill" is supposed to be taken within 72 hours of having sex. Sold under the name Plan B, it is not effective if pregnancy has already occurred, because it works by inhibiting or delaying ovulation.

About 460,000 women have taken Mifeprex safely in this country since it was approved, according to Danco Laboratories, the New York company that distributes the drug in the United States. Misoprostol, which is not a Danco product, has been in use since the mid-1980s. Though it was initially approved for prevention of gastric ulcers, it since has been prescribed for other purposes.

Outside California, other deaths have been reported in association with use of Mifeprex, and misoprostol. One occurred in Tennessee and five were reported outside the U.S., in Europe and Canada, say doctors familiar with the drugs. But only the Canadian death involved an infection.

So far, the CDC's McDonald said, just one thing ties California deaths together.

All the women who died, he said, took the follow-up drug, misoprostol, vaginally, instead of orally. It was an "off-label use," which is allowed but not specifically approved by the FDA on the basis of testing.

Cynthia Summers, Danco's director of marketing and public affairs, said that the company's sympathies were with the families of the women who have died but that no direct relationship between the drugs and the deaths has been established. In at least one Los Angeles County case, the coroner noted the use of the drugs but said the cause of death was undetermined.

"Physicians are free to prescribe FDA-approved drugs as they wish," Summers said. "Danco uses only the FDA-approved regimen in its labeling and promotional materials and does not promote any other regimens."

At least two of the women who died were prescribed the medications at clinics in the L.A. area. Patterson got the drugs at a clinic in the Bay Area city of Hayward. Authorities have not identified the fourth woman.

The unusual bacterium *Clostridium sordellii* was found in the bloodstreams of two of the four women who died of infection, Patterson and Chanelle Bryant, 22, of Pasadena. Investigators are trying to figure out whether the other two women also showed evidence of the bacterium, which McDonald said produces an effect akin to toxic shock syndrome.

"In the case of *Clostridium sordellii* and toxic shock in general," McDonald said, "it's a bacterium producing a toxin, which has some effect on the ability to maintain blood pressure. *Clostridium sordellii* produces two large toxins. Either or both of these affect the lining of blood vessels that keep fluid in the bloodstream."

Oriane Shevin, 34, of Sherman Oaks was the most recent woman to die, after she took Mifeprex and misoprostol to end a troubled pregnancy. The attorney and mother of two young children was taken by ambulance to Encino-Tarzana Regional Medical Center, where she died of sepsis, a blood infection, on June 14.

Dr. Philip Darney is a professor of obstetrics and gynecology at UC San Francisco, which has done extensive research on medical abortion, and he is not involved in the California investigation. He said that the way the drugs are administered is the likely culprit.

The FDA-approved regimen for a medical abortion is 600 milligrams of Mifeprex, the generic name of which is mifepristone, followed three days later by 400 micrograms of misoprostol. But most doctors in the United States cut the amount of mifepristone by two thirds — saying it is just as effective — and instruct women to take the misoprostol vaginally 24 hours later at home.

Darney said that European practitioners also reduce the amount of the first drug but seldom prescribe vaginal self-administration of the second. Studies have shown that taking the misoprostol vaginally makes the drug slightly more effective, so U.S. health officials will "have to decide if the slight increase in efficacy and convenience of vaginal self-administration is worth the very rare, unusual infection," Darney said.

Mifeprex, Darney said, has "gotten all the attention because it's been labeled the 'abortion pill.'… We think that an explanation for these unusual deaths — only one per 100,000 cases with this unusual organism — may be the vaginal self-administration of misoprostol under unusual circumstances. That might answer the very good question of why California, why not in Europe."

The only other known infection death involving the drugs occurred during a clinical trial in Canada in 2001. None of the European cases is believed to have been caused by infection, he said, adding that half of abortions in Scotland and one third of early abortions in France are done with the drug combination.

Lynn Bryant, whose otherwise healthy daughter Chanelle died in 2004, said that it is imperative for doctors, nurses and emergency room staff to know about the potential for serious side effects and death.

"I'd like people to know that it could be life-threatening, and also for the medical people to be

aware of the dangers of the drug when [women] come in for treatment," Bryant said.

Monty Patterson, Holly Patterson's father, believes that there is no way to administer Mifeprex and misoprostol safely, in part because it is impossible to tell the difference between the desired effects of the drugs and the signs of a serious infection. Women who take the drugs, he said, are told that they should expect abdominal pain and heavier bleeding than during a normal menstrual period, results that are similar to the drugs' danger signs.

In addition, the women who had *Clostridium sordellii* did not run a fever, a normal side effect of an infection, according to the FDA.

"That's a real issue where a woman, a young woman, has to figure out if she's beyond these so-called normal side effects … to serious adverse events," said Patterson, who has spent the last 22 months advocating against Mifeprex. "You have to figure it out, be able to call for help…. I feel the drug is not safe. There are problems. I feel a lot of these problems have not been reported."

Reporting deaths and side effects of the drug is voluntary for doctors, although it is a requirement for drug makers. Opponents of the drug believe that doctors are loath to report bad outcomes in abortion cases, making the number of problems far greater than the public knows. The FDA estimates that, in general, only about 10% of problems with drugs are reported.

Part of the investigation is a search for other deaths and additional ill effects from the drug combination.

"It may be that we've found all there are," McDonald said. "We don't know…. Until we've tried to draw the circle around the true number of cases, we can't get a sense of what the risk involved is."

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History of RU-486

The nonsurgical abortion drug has been controversial since it was created by French researchers a generation ago. The Food and Drug Administration recently launched an investigation into the drug regimen.

1980 — Researchers at Roussel Uclaf synthesize a drug that blocks the hormone needed to sustain pregnancy. Its generic name is mifepristone.

1983 — The Population Council, a nonprofit health research organization, gets FDA approval to test mifepristone in the U.S., and more than 300 women are given the drug during studies at USC.

1989 — Mifepristone becomes available in France, after extensive protests from anti-abortion

groups.

1991 — Mifepristone is approved for use in the United Kingdom. **1993** — President Clinton directs the Department of Health and Human Services to promote the testing, licensing and manufacture of mifepristone in the U.S.

2000 — The FDA approves mifepristone in September. Two months later, Danco Laboratories begins distribution of the drug under the brand name Mifeprex.

2001 — Brenda Vise, 38, of Chattanooga, Tenn., dies of a ruptured ectopic pregnancy after taking the drug combination. A Canadian woman dies of infection after that country's drug trials.

2003 — Holly Patterson, 18, of Livermore, Calif., dies of a blood infection after a medical abortion. A bill to establish Holly's Law, to take Mifeprex off the market and review its safety, is introduced in Congress.

2004 — Chanelle Bryant, 22, of Pasadena, dies of infection after a medical abortion.

2005 — Oriane Shevin, 34, Sherman Oaks, dies of infection after a medical abortion. The FDA sends out a public health advisory warning of the danger of infection when using Mifeprex and misoprostol. Calls resume for the passage of Holly's Law.